Adami (J. G.)

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Without doubt the most important fact elucidated by a study of the hepatic lesions of syphilis is that, from an anatomical and histological point of view, no distinction can be drawn between secondary and tertiary syphilis.

Clinically, I admit that such a distinction is useful, nor do I wish it to be thought for a moment that I imagine it can be done away with, although even clinically—as seen in connection with the syphilodermiæ—the establishment of a hard-and-fast demarcation between what is secondary and what tertiary leads not infrequently to confusion. The most that can be laid down is that when syphilis is acquired in the ordinary way, by sexual connection, the extension of the disease in general follows a definite course, the tissues tending to be affected in definite order. Or perhaps it is more correct to say that in syphilis, as in other zymotic dis-

* A contribution to the discussion upon syphilis at the New York Academy of Medicine, March 9, 1899.

eases—I use the term zymotic in its strict sense—there is a local or tissue predisposition, so that certain tissues are apt to be more extensively and more markedly affected than others, the virus multiplying more readily; so that in them, as a consequence, there is an earlier and more pronounced reaction.

But while this is the case, the reaction in a given tissue is of like order, be the period of local infection early or late; at most there may be histological differences caused by the age of the lesions and by variation in the interaction between virus and tissue. If the virus be strong, or the tissue be possessed of feeble reactive powers, the histological appearances differ to a greater or less extent from what is seen when the virus is weak or the tissue possesses originally or has acquired strong reactive power. And as a corollary to this, it may be said that where the virus is powerful and there is rapid proliferation there, in such diseases as syphilis and tuberculosis, the effects upon the tissues are modified so that we have to deal not solely or not in the main with the local disturbances caused by focal growth of the virus (infective granulomata), but see other well-marked anatomical changes, brought about by diffusion of the toxines. In other words, where the tissues are susceptible and the virus relatively powerful there may be generalized tissue disturbances apart from, and in addition to, the granulomatous developments directly caused by the focal proliferation of the germs. For at the start it must be laid down that, although as yet we are uncertain as to the exact causative germ of the disease, syphilis is a disease of microbic origin. The more one studies, the more is one convinced that the analogy between tuberculosis and syphilis is complete—only in the one

we have isolated and studied the germ, in the other we have not.

For what do we find with regard to the hepatic manifestations of syphilis? Let us first take those of the congenital disease. There are many reasons why these should be considered first: these were the first specific hepatic manifestations to be studied and clearly recognized; they are much more frequent and more extensive than are hepatic lesions in the disease of postnatal acquirement, and, death occurring very frequently within a month or two after birth, there is less uncertainty as to the period of development and duration of the lesions than there can be in the disease of adult life.

That the liver should be so frequently affected in this form of syphilis is easily understood if we remember that the specific syphilitic lesions of the newborn are congenital and not inherited, that the infection is through the placenta, and that, as a consequence, the infected blood coming from the placenta passes through the liver before it reaches the heart or any of the other tissues of the fœtal organism. Chiari's well-known observation may here be repeated—namely, that in a hundred and forty-four cases of infantile syphilis he found the liver affected, and that extensively, in a hundred and twenty-three, or nearly nine tenths. In the adult, on the other hand, both brain and testicle are more frequently the seat of extensive lesions, and when it is remembered how relatively common is tertiary syphilis and how relatively uncommon specific disturbances of any of these three organs the contrast between the frequency of congenital and acquired hepatic disturbances become more manifest. At the same time I am not prepared to accept Fournier's statistics as perfectly reli-

able; careful observation of 3,429 cases of tertiary syphilis should surely reveal clinical evidence of more than nine cases of hepatic implication.

This is not the place for me to dwell upon the vulgar error of speaking of *inherited* instead of *congenital* syphilis; suffice it to say that Gärtner's * *reductio ad absurdum* of the inheritance, so called, of paternal tuberculosis must hold equally for syphilis.† Indeed, were it possible for the bacillus or germ of syphilis to be present in the ovum at the moment of fertilization, to lie latent during the embryonic period and only to cause reaction during fœtal life, that is to say, after the different organs have assumed the form and structure which will pertain to them through postnatal existence, even then such presence of the germ would not be true inheritance—it would be an epiphenomenon; for true inheritance demands the carrying over of features peculiar to the germ plasm of the parents. The fortuitous inclusion of a microbe in one particular ovum is not a matter of inheritance.

The different forms of lesions due to syphilis to be met with in the infant's liver are, I think, included in the following list:

I. Well-defined gummata.

II. Miliary gummata with generalized fibroid change affecting circumscribed areas of the liver.

III. Admixture of miliary gummata and generalized fibrosis affecting the whole organ, which is in consequence enlarged.

* Gärtner. *Ztschr. f. Hygiene*, xiii, 1893, p. 101.

† By this I do not mean to infer that there is no indirect inheritance. Probably the majority of Fournier's *parasyphilitic* lesions, if not all, are examples of such indirect inheritance: stigmata are inherited, not the disease itself.

IV. Generalized atrophic cirrhosis without much evidence of gummata, but associated with icterus, œdema, etc., the organ being very granular and contracted.

Time forbids that I should quote examples of these different conditions. Quite the commonest is the second form, in which there are no well-developed gummata as generally understood, but on section through the affected areas numerous minute focal collections of small round cells are to be made out, invisible or just visible to the naked eye, and in their neighborhood extensive pericellular fibrosis, so that the organ presents a patchy appearance, paler areas of large size standing out against the darker red or liver-colored background of the unaffected tissue. Here we have to deal with a relatively early and progressive stage of disease in which there is little or no necrobiosis and development of gummy matter.

There are, however, fairly frequent cases on record of the development of true gummata, easily seen by the naked eye, some as large as an almond, recognized, not, I believe, in children born dead, but in those dying as early as two weeks after birth (Canton), and at times showing signs of contraction.

The relationship between these miliary gummata and the gross gummata of the liver is that between miliary tubercles and isolated caseous tubercles of the same organ. We never think of suggesting that the two latter forms of tubercle indicate different periods of the tuberculous process. At most we regard the first as of more acute, the second as of more chronic development. We know full well that miliary tuberculosis of the liver may develop at any stage of the disease, either soon after the primary infection or only as a terminal event after

long years of slow and, it may be, intermittent extension of the disease elsewhere. The fact that both gross and miliary gummata may occur in the liver of the newly born is an absolute proof that the two forms are not characteristic of two different stages or periods of the disease—"absolute," that is to say, unless we are prepared to admit that while certain tissues, such as the skin, present well-marked secondary lesions, others may present either secondary or tertiary changes. If we do this, then the use of the terms becomes almost meaningless. For it must be kept clearly in mind that while the livers of these syphilitic infants show extensive fibrosis and indications which usually are recognized as of tertiary type, the cutaneous eruptions are of the nature of secondary manifestations.

But over and above the granulomatous changes in the infant's liver it is most noticeable that a more generalized affection is the characteristic feature—namely, fibrosis affecting either the whole organ or larger or smaller areas. Such fibrosis might be due to various causes; indeed, our knowledge of the ætiology of cirrhotic changes in the liver, as in the kidney, and our knowledge of fibrosis in general, is not sufficiently advanced to permit us to make positive statements. And yet, since 1896, when in this very room, although not before your society, it was my privilege to deliver the Middleton-Goldsmith Lectures,* and I discussed the pathology of fibrosis, some little advance has been made in our conception of the process. For, on the one hand, Flexner † has shown that toxic substances (the blood

* *Medical Record*, 1896.

† Flexner. *Transactions of the Pathological Society*, Philadelphia, 1896.

serum of another animal) may lead to the development of cirrhosis, and, on the other, Weaver,* of Chicago, within the last few weeks, working (I think I may say) along lines suggested by certain publications of mine, has demonstrated that bacteria exist which directly induce hepatic cirrhosis. Thus it would seem that whether in the process of excretion of toxic substances by the liver cells, or by the taking up of certain bacteria and the influence of their toxines when so taken up, the liver cells may undergo a parenchymatous degeneration so intense that death ensues, and following thereupon a replacement fibrosis occurs, more or less pure and unaccompanied by acute inflammatory change according as to whether the parenchymatous disturbance is unaccompanied by interstitial irritation or no. Where many miliary gummata are present much fibroid change is eventually brought about by the tissue changes which follow their development.

We are not as yet in a position to state whether the fibroid change of this type in the liver of the syphilitic child is a consequence of the attempted removal of the syphilitic germs from the portal circulation by the agency of the endothelium of the hepatic blood-vessels and by the liver cells, or whether it is purely the circulating toxines of the disease that cause the disturbance. To me it would seem that one or other of these causes must be at work. The pericellular character of the cirrhosis is against the change being in the main a fibrosis following upon round-celled and miliary gummatous infiltration, while the fact that the change may affect the whole organ, as again the very extent of the areas when the whole organ is not affected, is quite opposed

* Weaver. *Philadelphia Medical Journal*, February 4, 1899, p. 283.

to the view that we have to deal with primary focal necroses, such as are to be met with in typhoid and other acute infective diseases, or in infarctous disturbances.

If Marchand's * cases of atrophic granular cirrhosis occurring in fœtuses born dead are, as he holds, of syphilitic origin, they afford evidence of the extreme results of such fibrosis following upon generalized syphilitic parenchymatous hepatitis.†

Thus, to sum up the broad features characterizing the syphilitic manifestations in the infant's liver:

1. Syphilis may lead either to granulomatous deposits in the organ or to interstitial fibroid changes.

2. The specific granulomata may be present either in the form of minute multiple miliary gummata, or of isolated larger gummata, such as in general are regarded as being of tertiary nature.

3. It is not possible to regard the one form as secondary, the other as tertiary, for either may exist with cutaneous disturbances of the secondary type.

4. By analogy, the interstitial fibroid change, so common in infantile syphilis, would appear in the main to be secondary to a degeneration and necrosis of the hepatic parenchyma, induced by the action of the toxines of the syphilitic virus upon the individual liver cells. In part it is developed in direct association with the development of miliary gummata.

Passing now to the hepatic disturbances in syphilis of postnatal acquirement, we find it more difficult to de-

* Marchand, *Ctrlbl. f. allg. Pathol.*, vii, 1896, p. 273.

† Dr. Jacobi tells me that he has described one of these cases of atrophic cirrhosis in the infant; like Marchand, he was forced to conclude that it must have been of syphilitic origin.

termine the age and duration of the lesions found, a difficulty due to the fact that syphilis is not in itself a cause of death during the months which immediately follow infection. I know of no adequate study made upon the livers of those who, suffering from well-marked secondary symptoms, have succumbed to intercurrent disease or accident. A thorough investigation of the visceral changes occurring in the secondary period remains as much a desideratum to-day as it was in the seventies, when Jonathan Hutchinson called attention to this gap in our knowledge. It is, however, probable that in the vast majority of cases the liver is not gravely affected during this stage, for otherwise it is most unlikely that with the vast number of autopsies made annually a fair number of instances of death during this period should not have been investigated; so that any marked departures from the normal in the condition of the organ should by now have gained recognition. It is equally true that there might be a certain amount of disturbance—the existence of miliary gummata, or, again, of a moderate extent of parenchymatous degeneration—which might easily escape detection, or be ascribed to other causes.

Some few cases are on record of extensive hepatic derangement during the secondary state. Thus, Hilton Fagge* reports the case of a female of twenty-three years in whom there was a history of syphilitic rash with loss of hair and macular syphilides; jaundice supervened and the patient became drowsy and comatose. At the autopsy, the liver, which weighed forty-six ounces, was of an opaque bright yellow color and of dense consist-

* Hilton Fagge. *Transactions of the Pathological Society*, London, xviii, 1867.

ence. The surface was mottled, the left lobe resembling very closely that of the infantile syphilitic liver. On section the organ appeared pale and semipellucid, and macroscopically the parenchyma was seen to be replaced by connective tissue. Unfortunately, the description given does not extend to full details. But clearly here is a case of generalized cirrhotic change in secondary syphilis not unlike that found in the infantile disease.

Somewhat similar cases are recorded by Engel-Reimers,* Kratz,† and Neumann.‡ In all these cases there was a condition not unlike subacute yellow atrophy. Engel-Reimers considered the condition due to enlarged lymph glands at the hilus. While these might cause icterus, it is difficult to see how they could bring about a general atrophic condition of the organ; the explanation is clearly inadequate. Neumann's case is distinctly interesting; it is that of a man of twenty years, ill for about eight months. When seen, in March, 1894, there were papules on the external genitalia and buccal mucosa, and a slight icterus. The jaundice became intense, with great abdominal pain and ecchymoses. The liver diminished, and in nineteen days the patient died with uræmic symptoms. To me the special interest lies in Kolisko's diagnosis at the autopsy, which was that of "catarrhal icterus with cholæmia; regeneration of the hepatic parenchyma in the form of adenomatous tumors, following upon acute atrophy of the same." Here was evidently acute generalized hepatitis.

* Engel-Reimers. *Jahrb. d. Hamburger Staatskrankheitanstalten*, 1889.

† Kratz. 66. *Versamml. d. Naturforsch.*, Vienna, 1894 (Path.-anat. Section).

‡ Neumann. Nothnagel's *Specielle Pathologie*, xxiii, p. 409. I am indebted to Neumann for the two previous quotations.

According to Neumann, Dittrich collected forty-six cases of syphilitic hepatitis, and these in the main were from the secondary period of the disease. An observation by Bec * would seem to indicate that such hepatitis, even when somewhat chronic, often leading to extensive trouble, may undergo complete absorption, or, at least, may be followed by no gummatous development.

It will be noticed that in the above cases jaundice manifested itself. Now jaundice is a not uncommon event in secondary syphilis. Attention has frequently been called to its existence from the time of Ricord and Gubler onward; Lancereaux alone collected twenty-one cases. Within the last two years Neumann, Joseph, and Uhlmann have redirected attention to its prevalence. I can not but think that this jaundice must afford another indication of what I have already dwelt upon in connection with infantile syphilis—namely, that the liver, being a great excretory organ, may in certain cases be so injured by the action of syphilitic toxines that parenchymatous and, it may be, catarrhal hepatitis is set up and the jaundice be an indication of the functional disturbances due to this cause. This view appears to be more probable than either of the other suggested explanations, which are that the jaundice is obstructive and due either to specific growths in the bile ducts, or to the pressure of enlarged lymph glands at the hilus of the liver upon the larger bile passages.†

We thus, even in the early stages of the disease of postnatal acquirement, obtain evidence pointing to the

* Bec. *Gaz. méd. des hôpit.*, lviii, 1885, p. 140.

† Neumann (*loc. cit.*) gives a full and interesting study of specific icterus.

existence of generalized effects of syphilis upon the organ. As I have pointed out elsewhere,* a fairly extensive fibrosis, apparently independent of the gummatous developments, is not infrequently to be met with in cases where there is active progressive syphilis long years after primary infection.

Turning now to the more generally recognized evidence of syphilis affecting the liver in the tertiary stage —namely, the gummata—and discussing first the large gummata, which are the most characteristic lesions of acquired syphilis, it must be clearly borne in mind that two distinct conditions are popularly confounded together and both regarded as tertiary manifestations—namely, the fibroid pittings and cicatrices which are the final indications of gummatous deposits in the liver, which remain after complete absorption of the original gummatous mass. We not infrequently come across these disfigurements and distortions in the liver in the bodies of those who for years have presented no indications of active syphilis, and they must, I hold, be regarded as obsolete gummata. Indeed, in one case, upon making microscopic sections through a most characteristic puckering, I found scarce any fibroid tissue left; that also had undergone absorption. On the other hand, we have to recognize gummata with cheesy or gummy contents surrounded by fibrous tissue, which are latent or obsolescent, and others again presenting like characters, but surrounded by hepatic tissue, which under the microscope presents infiltration with small round cells and evidence of progressive syphilis. It is these latent and active gummata which alone are of any importance,

* Adami. *Montreal Medical Journal*, xxvii, 1898, p. 413.

for both indicate that the disease, to say the least, has not been eradicated from the system.

The important point to notice is that in one liver we at times meet with all the forms above mentioned. I have come across cases at autopsy showing well-marked cicatrices and puckerings of practically obsolete gummata, large, well-defined gummata with necrosed centres, and, upon studying the sections of the liver from the neighborhood of the latter, I have there seen the irregular minute collections of small round cells which, in an infant's liver, we would have had no hesitation in describing as miliary gummata. These appearances I have seen in the liver of a man dying apparently only between two and three years after primary infection, as again in the liver of another infected fourteen years before death.

The evidence before us all points to the fact that in the adult, as in the infant's liver, gummatous development may occur at any period after the disease has become generalized throughout the body.

From what has already been stated, it follows that the same lesions are to be met with in the adult liver as are recognizable in the organ affected by antenatal disease. There may be:

I. Large well-formed gummata.

II. Miliary gummata.

III. Acute parenchymatous hepatitis (with jaundice).

IV. Syphilitic cirrhosis.

But clearly the element of time introduces frequently a difference and appearances not seen in the infantile liver. Thus we encounter in addition:

V. Obsolescent gummata: large gummata under-

going involution and absorption, with surrounding and limiting fibroid change and contracture. This is the lesion most often met with, and most typical of the syphilitic liver of the adult.*

VI. Obsolete gummata, represented by puckering and deformity of the organ, with a relatively small amount of fibroid growth radiating from the seat of the previous gummatous formation—and by nothing else.

VII. A further lesion, which must be referred to here—one not seen in the infant †—is the development of tumorlike outgrowths, so sharply defined and so large as not infrequently to lead to the false diagnosis of malignancy. The structure of these masses affords ground for believing them to be the outcome of a slowly progressive centrifugal infection of the liver tissue from an original isolated gummatous focus (or small collection of neighboring specific tubercles), with associated reactive hyperplasia of the liver tissue at the periphery; progressive infiltration of the newly formed parenchyma by miliary gummata and eventual replacement of these last by fibrous connective tissue; so that microscopically these tumorlike outgrowths present an outer layer of liver tissue, infiltrated by collections of small cells, inclosing a dense mass of fibrous tissue with more or less "gummy" degeneration.

Time, therefore, is an element causing difference in

* What is the causation of the coarse bands of fibrous tissue radiating from these obsolescent gummata I must leave an open question. It has been suggested that they indicate a tendency for the fibroid change to be developed along the course of the main lymphatic vessels leading from the gummatous focus.

† In this I am mistaken. I owe to Dr. Jacobi (verbal communication) a reference to a case by Cohn (?) of one of these tumorlike formations in the infant presenting all the features here described.

the appearances of the adult and infantile lesions. But this is not the only one. The other, and yet more distinctive, is the predominance of generalized fibrosis in congenital syphilis, of focal granulomatous changes in the syphilis of adults.

The explanation of this difference would seem to be that the young liver cell is more susceptible and less resistant to injuries inflicted by toxic substances; it is more prone to degenerate; and, if the view here enunciated be correct (namely, that the fibrosis is largely of the "replacement" type), we have in this feebleness of the young liver cell a sufficient explanation why fibrosis here predominates. With the adult cell it is different. Inasmuch as a main function of the liver is to eliminate toxic substances from the circulating blood, its cells with advancing life become capable of withstanding toxines to a relatively very considerable extent. It is, indeed, remarkable to observe what extreme degenerative changes of the cloudy and even of the fatty type may be observed in the liver cells of an adult rabbit—for example, a few hours after intravenous inoculation of a centimetre of a culture of such a form as the colon bacillus; and yet in the course of a few days (as determined in other rabbits similarly treated) the liver cells may have completely recovered and show no signs of the intense disturbance set up by flooding the system which the bacilli and their toxines.

Thus in the adult (as distinguished from the senile) there is not the tendency for the extreme fibroid change to manifest itself under the action of irritants, which in the young lead to the production of the same.

It may be asked why the liver of the newly born infant more than other organs is susceptible to these de-

generative changes. There are, it seems to me, two main reasons: 1. The liver is especially concerned in elimination of toxic substances, and its cells bear the brunt of intoxication by the syphilitic virus. 2. Placed, as it is, between the placenta and the general circulation of the fœtus, its cells tend to eliminate toxic materials brought by the umbilical vein; in this way, again, they bear the brunt of intoxication, and at the same time reduce the amount of toxic material capable of acting deleteriously on the other organs. But it must be remembered that other fœtal organs may also show fibroid changes.

There is one other factor in the production of specific lesions which so far I have not touched upon, one which, judging from studies made, more especially upon the syphilitic heart and brain, may very possibly be of signal importance. I refer to arterial change—endarteritis and periarteritis. We know, however, practically nothing concerning the part played by this in hepatic lesions. I can therefore mention it and pass it by.

Hence, to sum up: While the changes seen in the adult and infantile syphilitic livers are ætiologically and anatomically identical, they may present differences due in part to their relative duration, in part to the reactive powers of the hepatic parenchyma at different life periods.

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